IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of: Dale B. Schenk et al. Application No.: 10/777,792 Filed: February 11, 2004 For: PREVENTION AND TREATMENT OF AMYLOIDOGENIC DISEASE Customer No.: 00826	Before: Grimes, Fredman and Walsh, Administrative Judges Technology Center: 1600 **REQUEST FOR REHEARING UNDER 37 C.F.R. 41.50(b)(2)**

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Commissioner for Patents
P.O. Box 1450
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Sir:

Further to the Decision on Appeal of August 30, 2010 and in accordance with the provisions of 37 C.F.R. § 41.52, appellant requests rehearing in the above-captioned application.

The Board has subdivided the rejection into four issues at page 6 of its decision. Appellant will address its comments by reference to the first and fourth of these issues.

Whether it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of Wong and Selkoe to make a conjugate comprising an Aβ1-7 fragment

The lynchpin of the Board's conclusion that it would have been obvious to replace Wong's Aβ1-10 fragment with an Aβ1-7 fragment is its interpretation that Selkoe's teaching to use a fragment of "about 8 or more residues" must be interpreted to include a fragment having seven residues. The Board says such an interpretation is compelled because otherwise the word "about" would be superfluous (Decision at p. 8, 2nd paragraph).

In reaching this conclusion, appellant respectfully submits that the Board has overlooked an alternative and more likely interpretation of the word "about." The Board's interpretation views "about" as qualifying 8 amino acids only on the lower end, so as to imply fragments of seven or eight amino acids are equally applicable. However, the word "about" is more reasonably interpreted to include some measure of variation in both directions around 8 amino acids, in other words 7, 8 or 9. By effectively describing minimum length by a range around 8 rather than a single value, Selkoe is conveying that the minimum length cannot be defined with absolute certainty. In other words, a minimum length of about 8, could for example be 7, 8 or 9, perhaps depending on the circumstances. A teaching that there is some margin of uncertainty in the length of a minimum fragment and that 7 residues lies toward the edge of what might be feasible does not mean that an Aβ1-7 fragment would necessarily fail, but does suggest there is some risk of failure in an Aβ1-7 fragment or a need to expend more effort to generate a suitable antibody that would not be present in using the Aβ1-10 fragment.

The Examiner in fact agreed with appellant's interpretation of the phrase "about 8 or more residues:"

> "...applicant states that a "fair reading of Selkoe's comment that a fragment of about 8 or more residues can be used for generating antibodies is that a fragment of 8 residues is about the minimum size and that if a smaller fragment is used there is at least a risk of

failure." (remarks, p. 8, emphasis added) *The examiner agrees; this is precisely the point.*

Office action of November 18, 2008 at p. 6 (emphasis added).

However, the Examiner maintained the rejection presumably on the basis that there was still a reasonable, albeit diminished, expectation of success.

The PTO's 2010 Examination Guidelines for Determining Obviousness (Fed. Reg. 75:169 (September 1, 2010) pp. 53643-53660 at p. 53646) state that "when a combination invention involves additional complexity as compared with the prior art, the invention may be nonobvious unless an examiner can articulate a reason for including the added features or steps. This is so even when the claimed invention could have been readily implemented." This principle derives from the case, *In re Ommeprazole Patent Litigation* 536 F3d 1361 (Fed. Cir. 2008).

Here, the claimed invention involves the additional complexity presented by a possible risk of failure or additional effort without any compensating advantages. By selecting an Aβ1-7 fragment rather than Aβ1-10, the best the artisan could have hoped to achieve would be to produce an antibody with essentially the same properties as resulted from immunizing with Wong's Aβ1-10 fragment. However, the artisan would have been assuming an unnecessary risk of failure or expenditure of greater effort to generate a suitable antibody not present were Aβ1-10 fragment or many other fragments of Aβ selected. Given the assumption of unnecessary complications, appellant maintains that no or insufficient reason has been provided for specific selection of an Aβ1-7 fragment rather than Aβ1-10 or many other possible alternative Aβ fragments whose lengths would not present any concerns with respect to generating a suitable antibody.

Whether appellant has established that the claimed invention provided unexpected results sufficient to rebut a prima facie case of obviousness.

Appellant has provided evidence that the Aβ1-7 moiety of the claimed conjugate has an unexpected advantage relative to the Aβ1-10 fragment used by Selkoe. Briefly to recap from the appeal brief and reply brief, the unexpected advantage of the claimed conjugates vis-a-vis

Wong's1-10 fragment is supported by three pieces of evidence. First, the specification shows that three epitopes predominantly responsible for plaque clearing effects occur within residues 1-7 of Aβ (Table 16 of specification). Second, the art has reported minimum T-cell epitope size of about 9 amino acids (Rammensee, *Curr. Opin. Immunol.*, 1995, 7:85-96 at p. 89, paragraph bridging cols. 1-2). Third, post filing clinical trials have indicated a side effect in a small proportion of patients receiving unconjugated Aβ (residues 1-42) is likely mediated by T-cells (Gilman et al., *Neurology*, 64:1553-1562 (2005) at p. 1561, second col., 2nd paragraph; Greenberg et al., *Nature Medicine*, 9(4):389-390 (2003), at paragraph bridging 389-390; as well as references cited in appeal brief at p. 13, first paragraph of appeal brief). In the aggregate, these reports provide evidence that an Aβ1-7 fragment is likely to be equally effective as an Aβ1-10 fragment in inducing three classes of antibodies primarily responsible for plaque clearing but even less likely to have T-cell mediated side effects because of its smaller size relative to the approximate minimum size of T-cell epitopes reported by Rammensee. This evidence supports the teaching of reduced side effects disclosed in the specification (*see* p. 13, first paragraph).

The Board's dismissal of this evidence (Decision at pp. 9-10) on the basis that the evidence was not generated using the claimed conjugate and that appellant is arguing the advantages of different products is respectfully submitted to indicate a misapprehension of the nature of the unexpected result and the evidence supporting it.

Appellant has never contended that the underlying evidence was generated using a conjugate as claimed. Nevertheless, the evidence inferentially supports a conclusion that the Aβ1-7 moiety of the claimed conjugates has an unexpected property of practical importance vis a vis the Aβ1-10 fragment of Selkoe. Table 16 of the specification shows that monoclonal antibodies 3D6, 10D5 and 22C8 with epitope specificities of Aβ1-5, Aβ3-6 and Aβ3-7 respectively were effective in phagocytosis of plaques. Similar results were obtained for polyclonal sera to Aβ1-5, 1-6 or 3-7. By contrast, antibodies 6E10 and 14A8 with specificities of Aβ5-10 or 4-10 bound to plaques but were not effective in phagocytosis. Antibodies binding to mid and C-terminal epitopes were also found not to phagocytose plaques. Together, these data provide evidence that the principal epitopes responsible for plaque clearing occur with residues 1-7 of Aβ. It is immaterial to the conclusion regarding the location of epitopes that the

data are based on use of monoclonal or polyclonal antibodies rather than conjugates. It is also immaterial that the monoclonal antibodies were not produced by the claimed conjugates. All that is relevant is that the data imply that the principal epitopes responsible for plaque clearing occur within residues 1-7 of Aβ. The Board has provided no reason to disagree with such a conclusion from the data.

The above data, albeit not generated with the claimed conjugates, provide inferential evidence that the Aβ1-7 moiety of the claimed conjugate includes all of the principal epitopes responsible for plaque clearing present in Aβ1-10 notwithstanding its smaller size. At the same time, the smaller size has a practical advantage in reducing the potential for side effects. The advantage in avoiding side effects arises because a reduction in size from ten to seven amino acids makes a peptide too short to include the minimum of 9 amino acids required for a T-cell epitope (Rammensee, supra). A clinical trial resulting from immunization with full-length Aβ was halted because of a side effect occurring in about 5% of subjects believed to be mediated by T-cell epitopes on Aβ (see Gilman or Greenberg, supra). Reducing the size of Aβ to a length too short for a T-cell epitope effectively eliminates the risk of such side effects.

In the aggregate, the evidence indicates that an Aβ1-7 fragment includes the same principal epitopes responsible for clearing plaques as Aβ1-10, and because of its smaller size has potential for reduced side effects. There is no evidence prior to the priority date of the application to suggest that residues 8-10 of Aβ could be dispensed with and still leave intact the principal epitopes for plaque clearing. There is also no evidence prior to the priority date of the application that would have suggested that a reduction of size from Aβ1-10 to Aβ1-7 would have had a practical advantage in avoiding a significant side effect. Thus, the Aβ1-7 fragment can only be regarded as having unexpected advantages for clinical use vis a vis Aβ1-10.

To reiterate, appellant is not arguing about the advantages of different products, but instead is using the data in the specification defining the location of epitopes responsible for side effects and postfiling data regarding side effects to support an inferential conclusion of unexpected results of practical significance of the Aβ1-7 moiety of the claimed product vis a vis Wong's Aβ1-10 fragment.

It is unclear if the Board also adapted the Examiner's position that the unexpected results can be disregarded because they relate to a use of the claimed product (Examiner's answer at p. 8, last paragraph). In this connection, appellant reiterates that advantages of a product in use are relevant to the product itself when the advantages stem directly from the product. "[A]dvantages...do not properly belong in the claims, the sole function of which is to point out distinctly the process, machine, manufacture or composition of matter which is patented...not its advantages.. It is entirely proper, nevertheless, in evaluating nonobviousness...to take into account advantages directly flowing from the invention patented." *Preemption Devices v. Minnesota Mining & Manufacturing Co.*, 732 F.2d 903, 907 (Fed. Cir. 1984).

Evidence that a composition is "unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." MPEP § 716.02(a)(II). Generally, a showing of unexpected advantage is sufficient to overcome an obviousness where the unexpected advantage has practical significance greater than a known, expected result. *In re Nolan*, 193 U.S.P.Q. 641, 645 (CCPA 1977) (weighing, in determination of obviousness, expected and unexpected results based on their relative significance to operation of claimed invention).

Here, assuming for sake of discussion that sufficient rationale for combining the references for prima facie obviousness exists, the rationale lacks any practical significance. The Board's finding that a prima facie exists is not based on any specific teaching favoring an Aβ1-7 fragment over the Aβ1-10 fragment of Selkoe or any other Aβ fragment but rather on the proposition that Aβ fragments in general represent equivalents of Aβ1-10 for purposes of generating antibodies to Aβ for diagnostic uses. Thus, by selecting Aβ1-7 over Aβ1-10, the artisan would be engaging in variation only for variation's sake with a view to obtaining an antibody of similar utility to that already possessed.

By contrast, the data in the specification and post-filing data regarding side effects provide evidence that the Aβ1-7 fragment includes the same principal epitopes responsible for plaque clearing as Aβ1-10 notwithstanding its smaller size and at the same time has practical advantages of ease of avoiding side effects. By contrast, there was no benefit of substantial

practical significance apparent to the artisan from changing from Aβ1-10 to Aβ1-7, and in fact in appellant's view there was a unnecessary risk of failure or at least greater effort. Thus, assuming a prima facie case has been established, it is submitted to have been overcome by the evidence of unexpected results.

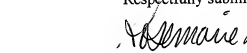
Although the Board has considered whether it was prima facie obvious to replace the carrier KLH with a toxoid from a pathogenic bacterium (Decision bridging pp. 8-9), the Board has overlooked or at least failed to address in its Decision appellant's position that the replacement confers an unexpected result that the claimed conjugates are rendered more suitable for human therapeutic use (appeal brief at p. 12, second paragraph, reply brief at pp.3-4, bridging paragraph). A toxoid from a pathogenic bacteria is more suitable for human use whereas KLH is a preferred carrier for animal use (*see* Penney, col. 2, lines 5-8; and col. 5, lines 4-12). Although the advantage of toxoids from pathogenic bacteria for human use is not itself unexpected having already been reported by Penney, the advantage of the claimed conjugates is unexpected because the cited art did not teach that the claimed conjugates had any use in humans. Without the insight provided by the present application that the claimed conjugates have a therapeutic use in humans, the claimed conjugates would have appeared disadvantageous relative to those of the art because the art was already using the preferred carrier for animal use. The advantageous property of the claimed conjugates of improved suitability for use in humans vis-a-vis the cited art can only be viewed as unexpected.

Appellant also argued that replacing Freund's adjuvant with QS-21 conferred an unexpected result of suitability for human use (appeal brief at p. 16, second paragraph). The Board dismisses this position as "misdirected and insufficient to overcome prima facie obviousness for the reasons already discussed" (Decision at p. 11, first paragraph). However, the only previous discussion of unexpected results is the Board's dismissal of an unexpected result relating to the Aβ1-7 moiety of the conjugate because the argument allegedly relates to a different product than that claimed (Decision at pp. 9-10). The Board's comments have no apparent relevance to the distinct unexpected result relating to the inclusion of QS-21 in the claimed composition, which does not rely on the data in Tables 16 and 17. Thus, it appears that the Board has misapprehended the nature of the unexpected result relating to QS-21.

As discussed in the appeal brief (p. 16, paragraph 3) and not contested by the Examiner's answer, whereas QS-21 is suitable for administration to humans, Freund's adjuvant is not routinely administered to humans because of toxicity, and instead is the most commonly used adjuvant for animal use. Assuming, as found by the Board, that it would have been prima facie obvious to replace Freund's adjuvant with QS21 with a view to generating antibodies in an animal, an unexpected advantages arises in that the use of QS21 renders the conjugate suitable for use in humans. The benefit in humans is unexpected not because QS-21's suitability for use in humans was unknown (this being reported by Hancock) but because Aβ1-7 was not known to have any therapeutic use in humans. The claimed composition including QS-21, has a new and unexpected use, *i.e.*, therapeutic use in humans, for which Wong's composition was not suitable because of the toxicities of Freund's adjuvant.

Reconsideration is respectfully requested for all of the above reasons.

Respectfully submitted,



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